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EXAMINER	
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ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/659,295	SCHAEBITZ ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,9,11-14,16-19 and 105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,9,11-14,16-19 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 30 July 2007 is acknowledged. Claims 2-4, 8, 10, 15 and 20-104 are cancelled. Claims 1, 5-7, 9, 11-14, 16-19 and 105 are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112, first paragraph

The rejection of claims 2, 3, 4, 8, 10, 15 and 101-102 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of GMCSF or GCSF, erythropoietin (EPO) for the treatment of stroke or cerebral ischemia and diseases enabled by the prior art, does not reasonably provide enablement for the methods as broadly claimed as set forth at pages 3-8 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' cancellation of claims 2, 3, 4, 8, 10, 15 and 101-102.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 3, 5, 6, 7, 9, 10, 17, 18, 101 and 105 under 35 U.S.C. 102(b) as being anticipated by Takeshi et al. (JP5246885A2, published 26 December 1991—provided on Applicants' 1449 form. Translation also provided by Applicants) as set forth at pages 8-10 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the claims to recite

treatment of "traumatic brain injury" (TBI), and Applicants' cancellation of claims 2, 3, 10 and 101. Note that the definition of TBI found at the website at ninds.nih.gov/disorders/tbi/tbi.htm reads:

> Traumatic brain injury (TBI), also called acquired brain injury or simply head injury, occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object, or when an object pierces the skull and enters brain tissue. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain. A person with a mild TBI may remain conscious or may experience a loss of consciousness for a few seconds or minutes. Other symptoms of mild TBI include headache, confusion, lightheadedness, dizziness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, a change in sleep patterns, behavioral or mood changes, and trouble with memory, concentration, attention, or thinking. A person with a moderate or severe TBI may show these same symptoms, but may also have a headache that gets worse or does not go away, repeated vomiting or nausea, convulsions or seizures, an inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation.

And at the website at: cdc.gov.mill1.sjlibrary.org/ncipc/tbi/TBI.htm

> A traumatic brain injury (TBI) is caused by a blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain. Not all blows or jolts to the head result in a TBI. The severity of a TBI may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury.

Since Takeshi teach the administration of GCSF, GMCSF, and/or EPO for the treatment of cerebral vascular dementia or Alzheimers' Disease or AD (see claims 1-3; paragraphs [0002], [0005], [0006]), or vascular dementia is associated with cerebral ischemia (see paragraph [0002]), this cannot be reasonably interpreted as TBI, thus the rejection is withdrawn.

The rejection of claims 2, 3, 4, 8, 10 and 101 are rejected under 35 U.S.C. 102(e) as being anticipated by Chajut (US 2002-0198150 A1—listed on Applicants' 1449 form—filed 7 June 2002, and also claiming priority to provisional application 60/296,585, filed 7 June 2001) as set forth at pages 11-13 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' cancellation of claims 2, 3, 4, 8, 10 and 101.

The rejection of claims 1, 2, 3, 4, 8, 9, 11, 12, 15, 16, 17, 18 and 105 rejected under 35 U.S.C. 102(a) as being anticipated by DE 100 33 219 A1 (published 24, January 2002, 7 days before the effective filing date of the instant application—listed on Applicants' 1449 form, translation of the relevant pages also provided by Applicant) as set forth at p. 13 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' filing of a declaration under 37 C.F.R. 1.132 stating that the disclosure of DE 100 33 219 A1 is Applicants' own work.

The rejection of claim 101 under 35 U.S.C. 102(b) as being anticipated by Konishi et al. (Brain Res. 1993; 609: 29-35—provided by Applicant on 1449 form) as set forth at p. 14 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' cancellation of claim 101.

The rejection of claims 1, 2, 3, 4, 5, 8, 9, 10, 18, 19 and 105 under 35 U.S.C. 102(b) as being anticipated by Buschmann et al. (WO 99/17798—provided by Applicants' on 1449 form) as set forth at p. 11 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the clams to recite traumatic brain injury or TBI and their cancellation of claims 2, 3, 4, 8 and 10.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 18, 19 and 105 under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 18, 19 and 105 in the rejection under 35 U.S.C. 102(b), and further in view of Siren et al. (Eur Arch Psychiatry Clin Neurosci. 2001; 251: 179-184) as set forth at pages 14-17 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the clams to recite traumatic brain injury or TBI and their cancellation of claims 2, 3, 4, 8 and 10.

The rejection of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 16, 18, 19 and 105 under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited above) and Siren et al. (cited above) as applied to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 18, 19 and 105 in the rejection under 35 U.S.C. 102(b), and further in view of del Zoppo GJ, Curr Opin Hematol. 2000; 7:309-15) as set forth at pages 17-18 of the

previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the clams to recite traumatic brain injury or TBI and their cancellation of claims 2, 3, 4, 8, 10 and 15.

The rejection of claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 13, 17, 18, 19 and 105 under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 17, 18, 19 and 10 in the rejection under 35 U.S.C. 102(b) and further in view of Emerich et al., Clin Pharmacokinet. 2001; 40: 105-23 as set forth at pages 18-20 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the clams to recite traumatic brain injury or TBI and their cancellation of claims 2, 3, 4, 8 and 10.

The rejection of claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 14, 17, 18, 19 and 105 under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—(cited above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 17, 18, 19 and 105 in the rejection under 35 U.S.C. 102(b), and further in view of Tarkowski et al. (Stroke. 1999; 30: 321-327—listed on Applicants' 1449 form) and Lu et al. (Neurobiology of Disease. 2001; 8: 194-206) as set forth at pages 20-21 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' amendment of the clams to recite traumatic brain injury or TBI and their cancellation of claims 2, 3, 4, 8 and 10.

The rejection of claims 101 and 102 under 35 U.S.C. 103(a) as being unpatentable over Konishi et al. as set forth at pages 21-22 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' cancellation of claims 101 and 102.

Double Patenting

The provisional rejection of claims 2, 3, 4, 8, 10, 15 and 101-102 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-22 and 52-53 of copending Application No. 10/880,101 as set forth at pages 22-24 of the previous Office action mailed 29 January 2007 is withdrawn in response to Applicants' cancellation of claims 2, 3, 4, 8, 10, 15 and 101-102.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 5-7, 9, 11-14, 16-19 and 105 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of GMCSF or GCSF, erythropoietin (EPO) for the treatment of stroke, cerebral ischemia, traumatic brain injury and diseases enabled by the prior art, does not reasonably provide enablement for the methods as broadly claimed as set forth at pages 3-8 of the

previous Office action (mailed 29 January 2007) is maintained for reasons of record and the following.

Applicants argue at p. 5, 2nd paragraph that they have more particularly defined the G-CSF derivatives in the claims.

Applicants cite case law at p. 6, 2nd paragraph to demonstrate that they have satisfied the written description requirement.

Applicants argue at p. 6, 3rd paragraph that they have described many examples of various G-CSF functional variants, muteins and mimetics in the specification, and Applicants provide additional examples of G-CSF derivatives at p. 6, last paragraph through p. 8, 1st paragraph.

Applicants argue at p. 8, 2nd paragraph, that "most neuroprotectants found to be effective in models of experimental stroke are also effective in models of experimental traumatic brain injury."

First, with respect to Applicants' argument that "most neuroprotectants found to be effective in models of experimental stroke are also effective in models of experimental traumatic brain injury," this is found persuasive as evidenced by Bouma et al. (Journal of Neurosurgery. 1992; 77: 360-368), who taught in 1992 that TBI and stroke share the same pathophysiological mechanisms (see abstract).

Applicants' other arguments have been fully considered, but are not found persuasive for the following reasons. In response to Applicants' argument that they have more particularly defined the G-CSF derivatives in the claims and that they have provided many examples of G-CSF derivatives, this argument is not persuasive. Although Applicants do provide a listing of possible muteins (for example, for G-CSF, see p. 21-24; for GMCSF, see 26-27), Applicants' own definition of derivatives encompass low molecular weight compounds (p. 22) and muteins having only 20-95% homology with the native proteins. In addition, the definition of a peptidomimetic is a

compound containing non-peptidic structural elements that is capable of mimicking or antagonizing the biological action(s) of a natural parent peptide, but does not have classical peptide characteristics such as enzymatically scissille peptidic bonds. In this case, the definition of derivatives provided by Applicants in the specification encompass almost any agent, including those yet to be discovered. The claims reciting GCSF, a G-CSF peptidomimietic, G-CSF comprising one or more chemical substituents, G-CSF fused to a second protein, a protein fragment of G-CSF having G-CSF activity or a modified polypeptide of G-CSF having G-CSF activity or combinations thereof amount to single means claims. Single means claims are those that cover every conceivable means for achieving the stated purpose. Single means claims are nonenabling for the scope of the claim because the specification discloses at most only those means known to the inventor, in this case, GCSF. When claims depend on a recited property, i.e, the ability to treat a neurological condition in this case, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See MPEP 2164.08(a). In addition, the introduction of 90% identity in the amended claims is too still too broad; 95% identity with an activity limitation more closely resembles the scope of what is enabled. In response to the case law cited by Applicants at p. 6, 2nd paragraph, it is noted that the claims were rejected under 35 U.S.C. 112, first paragraph for scope of enablement, not for written description, thus it is not relevant to the rejection of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The rejection of claims 1, 9, 17, 18, 19 and 105 under 35 U.S.C. 102(e) as being anticipated by Chajut (US 2002-0198150 A1—listed on Applicants' 1449 form—filed 7 June 2002, and also claiming priority to provisional application 60/296,585, filed 7 June 2001) as set forth at pages 11-13 of the previous Office action mailed 29 January 2007 is maintained for reasons of record and the following.

Applicants have filed an declaration under 37 C.F.R. 1.131 that prior to 7 June 2001 they had conceived and reduced to practice the invention using G-CSF for the treatment of stroke, Parkinson's Disease and Alzheimer's Disease, which is supported by the appended German Offenlegungsschrift DE 100 33 219 A1, filed 7 July 2000 in order to overcome this rejection.

The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Chajut US 2002-0198150 A1) reference. See MPEP 706.02:

> A rejection based on 35 U.S.C. 102(e) can be overcome by:
> (A) Persuasively arguing that the claims are patentably distinguishable from the prior art;
> (B) Amending the claims to patentably distinguish over the prior art;
> (C) Filing an affidavit or declaration under 37 CFR 1.132 showing that the reference invention is not by "another." See MPEP § 715.01(a), § 715.01(c), and § 716.10;
> (D) Filing an affidavit or declaration under 37 CFR 1.131 showing prior invention, if the reference is not a U.S. patent or a U.S. patent application publication claiming the same patentable invention as defined in 37 CFR 41.203(a). See MPEP § 715 for more information on 37 CFR 1.131 affidavits. ***When the claims of the reference U.S. patent or U.S. patent application publication and the application are directed to the same invention or are obvious variants, an affidavit or declaration under 37 CFR 1.131 is not an acceptable method of overcoming the rejection***. Under these circumstances, the examiner must determine whether a double patenting rejection or interference is appropriate. If there is a common assignee or inventor between the application and patent, a double patenting rejection must be made. See MPEP § 804. If there is no common assignee or inventor and the rejection under 35 U.S.C. 102(e) is the only possible rejection, the examiner must determine whether an interference should be declared. See MPEP Chapter 2300 for more information regarding interferences;
> (E) Perfecting a claim to priority under 35 U.S.C. 119(a)-(d) within the time period set in 37 CFR 1.55(a)(1) or filing a grantable petition under 37 CFR 1.55(c). See MPEP § 201.13. The foreign priority filing date must antedate the reference and be perfected. The filing date of the priority document is not perfected unless applicant has filed a certified priority document in the application (and an English language translation, if the document is not in English) (see 37 CFR 1.55(a)(3)) and the examiner has established that the priority document satisfies the enablement and description requirements of 35 U.S.C. 112, first paragraph; or
> (F) Perfecting *>benefit< under 35 U.S.C. 119(e) or 120, within the time periods set in 37 CFR 1.78(a) or filing a grantable petition under 37 CFR 1.78(a), by amending the specification of the

> application to contain a specific reference to a prior application or by filing an application data sheet under 37 CFR 1.76 which contains a specific reference to a prior application in accordance with 37 CFR 1.78(a), and by establishing that the prior application satisfies the enablement and written description requirements of 35 U.S.C. 112, first paragraph. See MPEP § 201.11 and § 706.02.

And MPEP 715:

> (B) To antedate a reference that qualifies as prior art under 35 U.S.C. 102(e), where the reference has a prior art date under 35 U.S.C. 102(e) prior to applicant 's effective filing date, and shows ***but does not claim the same patentable invention***. See MPEP § 715.05 for a discussion of "same patentable invention." See MPEP §706.02(a) and § 2136 through § 2136.03 for an explanation of what references qualify as prior art under 35 U.S.C. 102(e).

Note that because Takeshi ***claim*** the same invention, an affidavit or declaration under 37 CFR 1.131 is not an acceptable method of overcoming the rejection. See especially claims 1-6 of the Chajut reference, which recite:

1. A method for promoting recovery in a patient who has suffered a central nervous system injury, the method comprising administering to the patient a colony stimulating growth factor in a dosage sufficient to increase the number of bone-marrow-derived stem cells in the circulation of the patient, so as to thereby promote recovery in the patient.

2. The method of claim 1, wherein the colony stimulating growth factor is selected from a group consisting of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), stem cell factor (SCF), interleukin-3 (IL-3) and interleukin-6 (IL-6).

3. The method of claim 2, wherein the colony stimulating factor is G-CSF.

4. The method of claim 3, wherein the central nervous system injury comprises an ischemic episode.

5. The method of claim 4, wherein the ischemic episode is stroke.

6. The method of claim 3, wherein the ***central nervous system injury*** comprises a ***traumatic injury***.

New Rejections under 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 9, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—provided by Applicants' on 1449

form) in view of Bouma et al. (Journal of Neurosurgery. 1992; 77: 360-368). ***This rejection is necessitated by Applicants' amendment of the claims to recite treatment of traumatic brain injury (TBI).***

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The first factor considered when making a rejection under 35 U.S.C 103 is the scope and contents of the prior art. Buschmann et al. teach the administration of GMCSF and/or GCSF (either alone or in combination) via intravenous or peritoneal injection for the treatment of vascular disease or cardiac infarct or stroke (see p. 8, lines whole page; p. 10, 1st paragraph). Buschmann et al. contemplate the treatment of humans (see p. 18, 2nd paragraph). The second factor is to ascertain the differences between the prior art and the claims at issue. In the instant case, Buschmann et al. do not specifically teach the treatment of TBI. Nevertheless, Bouma et al. teach that TBI and stroke share the same pathophysiological mechanisms (see abstract; p. 366, right column, last paragraph) and that "further progress in the treatment of severe head injuries may be expected from therapies aimed at prevention of secondary ischemic insults and in the early interventions of cellular cascades initiated by ischemia." The third factor is to resolve the level of ordinary skill in the pertinent art. In the instant case,

the person of ordinary skill in the art (POSITA) is extremely high, as the POSITA is most likely an M.D. or Ph.D. engaged in clinical research. Finally, the Examiner must consider objective evidence present in the application indicating obviousness or nonobviousness. In the instant case, there is nothing in the instant application to indicate that treatment of TBI is non-obvious over treatment of stroke. On the contrary, Applicants state at p. 34 that "most neuroprotectants found to be effective in models of experimental stroke are also effective in models of experimental traumatic brain injury," thus this does not suggest any unexpected results over treating TBI vs. stroke. For these reasons, the POSITA, when reading the disclosures of Buschmann et al., who teach the treatment of stroke with GMCSF and/or G-CSF and Bouma et al., who teach that the pathophysiology of stroke and TBI are similar and suggest similar treatment approaches, would reasonably expect success in the treatment of TBI with GMCSF and/or G-CSF. In other words, the POSITA has good reason to pursue the known options within his or her technical grasp. In the instant case, the POSITA would be motivated to treat two conditions having similar pathophysiological mechanisms (i.e., TBI and stroke) in the same fashion. If this leads to the anticipated success, it is likely the product not of innovation, but of ordinary skill (the skill in the art is extremely high) and common sense.

Claims 1, 5, 6, 7, 9, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798) and Bouma et al. (both cited above), and further in view of Siren et al. (Eur Arch Psychiatry Clin Neurosci. 2001; 251:

179-184). In addition to what is discussed above the claims are further drawn to administering an additional hematopoietic factor that is EPO (claim 6) and that the hematopoietic factor is derived from a human factor (17). ***This rejection is necessitated by Applicants' amendment of the claims to recite treatment of traumatic brain injury (TBI).***

The combined teachings of Buschmann et al. and Bouma et al. are discussed above and are applicable here. Neither Buschmann et al. nor Bouma et al. specifically teach a human derived hematopoietic factor. However, Buschmann et al. do contemplate the treatment of humans and it would be obvious to use human-derived factors in the treatment of humans. In addition, with regard to claim 19, although Buschmann et al. do not specifically teach intracerebral administration of the hematopoetic factor(s), it would be obvious to do this since they contemplate treatment of stroke (i.e. brain injury) and intracerebral administraton would bypass the blood brain barrier. Furthermore, Buschmann et al. do not teach the administration of an additional hematopoietic factor which is EPO. Siren et al. teach at p. 182, right column, last paragraph to p. 183, left column, 1st paragraph that:

> The experimental data reviewed above demonstrate multiple neuroprotective mechanisms of action of EPO. These findings together with the fact that EPO and EPOR are expressed in the human central nervous system,...and that EPO is an extremely well-tolerated compound, used in millions of patients...,strongly support evaluation of EPO for neuroprotective therapy in a clinical setting. The therapeutic potential of this agent ranges from stroke and neurodegenerative diseases (Parkinson syndrome, Alzheimer's diseases, amyotrophic lateral sclerosis) to psychiatric applications such as schizophrenia, where neurodegenerative processes are likely to contribute to the pathophysiology of the disease...The initial safety study has been complete with promising results demonstrating that intravenously administered EPO is able to enter the

brain in acute human stroke victims and that the EPO treatment is extremely safe in stroke patients.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. by administering EPO for the treatment of stroke, as taught in Siren et al. because Siren et al. report success in their clinical trial in the treatment of stroke with EPO. The person of ordinary skill in the art would have been motivated to make the substitution because according to Siren et al. neuroprotection as a means to oppose pathological neuronal loss in diseases such as stroke is an approach that is well supported by data in the neuroscience field and administration of multiple factors that oppose neuronal loss would be beneficial. In addition, Buschmann et al. teach that the administration of CSFs leads to an increase in collateral vessels, which would improve outcome of diseases characterized by ischemia, such as stroke. Finally, Buschmann also teach that there is a need in the art for approaches to treating stroke or ischemic disease (p. 3, 2nd paragraph). Furthermore, the person of ordinary skill in the art could have reasonably expected success because both Buschmann et al. and Siren et al. report success in their methods. The combined teachings of Buschmann et al. and Siren et al. teach the administration of the same compounds to the same patient population, thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 5, 6, 7, 9, 11, 12, 16, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798), Bouma et al. and Siren et al. (all cited above) and further in view of del Zoppo GJ, Curr Opin Hematol.

2000; 7:309-15). In addition to what is discussed above the claims are further drawn to administering a hemodynamically active compound (11), tPA (12, 16). ***This rejection is necessitated by Applicants' amendment of the claims to recite treatment of traumatic brain injury (TBI).***

The combined teachings of Buschmann et al., Bouma et al. and Siren et al. are discussed above and are applicable here. The combined teachings of Buschmann et al., Bouma et al. and Siren et al do not teach the administration of tPA. del Zoppo teaches that as of the time of the invention (late 2000), tPA is the only agent licensed for clinical use in cases of acute ischemic stroke, (p. 311, left column, 2nd full paragraph). Because tPA breaks up clots, this relates to hemodynamics, or blood flow, the limitations of claim 11 are met. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. and Siren et al. by administering tPA to stroke, as taught in del Zoppo because according to del Zoppo, despite the clinical indications and patient limitations in the administration of tPA, tPA administration within 3 hours of stroke symptom onset increases the likelihood of no or minimal residual neurological outcome (see p. 313, right column, last paragraph), i.e., there are risks but the benefits to certain patients (minimal or no negative neurological outcome) recommend tPA for use in certain clinical cases of stroke. The person of ordinary skill in the art would have been motivated to combine the teachings because as outlined above, there are only a limited number of available options for the clinician in the treatment of stroke. Furthermore, the person of ordinary skill in the art could have reasonably expected success because both

Buschmann et al. and Siren et al. report success in their methods, and tPA was already used in the art in certain circumstances for the treatment of stroke. Finally, since Bouma et al. teach that the pathophysiology of stroke and traumatic brain injury are the same, the person of skill in the art would be motivated to administer tPA to those suffering from ischemia due to traumatic brain injury as well as ischemia due to stroke.

Claims 1, 5, 6, 9, 13, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798) and Bouma et al. (both cited above) and further in view of Emerich et al., Clin Pharmacokinet. 2001; 40: 105-23. In addition to what is discussed above the claims are further drawn to administering a compound that facilitates passage over the blood brain barrier (13). ***This rejection is necessitated by Applicants' amendment of the claims to recite treatment of traumatic brain injury (TBI).***

The teachings of Buschmann et al. and Bouma et al. are discussed above and are applicable here. Neither Buschmann et al. nor Bouma et al. teach administering an agent that facilitates passage over the blood brain barrier (BBB). Emerich et al. teach that the agent labradimil has been successfully developed to increase the permeability of the BBB (see for example, p. 119, left column, last paragraph, under "Clinical Results"). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. by administering labradimil as taught in Emerich et al. because Buschmann et al. teach administering CSFs via intraperitoneal or intravenous injection and they contemplate the

treatment of cerebral ischemia and stroke (discussed above), however, it is well known in the art that the BBB acts as a barrier to drugs getting to the brain (see for instance, Emerich et al., p. 106, right column, last paragraph). Emerich et al. remedies this deficiency and bypasses the need for direct intracerebral injection of CSFs by co-administering labradimil to temporarily increase the permeability of the BBB to drugs. The person of ordinary skill in the art would have been motivated to administer labradimil because it is well known that the BBB is a barrier to getting drugs to the brain and direct intracerebral injection is uncomforable. Emerich et al. state at p. 106, right column, last paragraph: "[b]ecause only a fraction of all bioactive drugs possess the attributes required to penetrate the BBB, the treatment of CNS disease could be improved if a means were available to safely and reversibly modulate the permeability of the BBB to allow greater drug distribution to the CNS." Furthermore, the person of ordinary skill in the art could have reasonably expected success because Emerich et al. teach that labradimil permeabilizes the BBB and could potentially be used to increase delivery of agents without increasing dosage (see abstract; citation above). Finally, since Bouma et al. teach that the pathophysiology of stroke and traumatic brain injury are the same and both occur in the CNS, the person of skill in the art would be motivated to administer an agent that eases permeability of the BBB to those suffering from ischemia due to traumatic brain injury as well as ischemia due to stroke. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 5, 6, 9, 14, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798 and Bouma et al. (both cited above) and further in view of Tarkowski et al. (Stroke. 1999; 30: 321-327—listed on Applicants' 1449 form) and Lu et al. (Neurobiology of Disease. 2001; 8: 194-206). ***This rejection is necessitated by Applicants' amendment of the claims to recite treatment of traumatic brain injury (TBI).***

The teachings of Buschmann et al. and Bouma et al. are discussed above and are applicable here. Neither Buschmann et al. nor Bouma et al. teach the additional administration of anti-apoptotic factors. Tarkowski et al. teach that there is decrease in expression of anti-apoptotic proteins in the cerebrospinal fluid of stroke victims (see p. 325, right column, last paragraph) and concluded that controlling or down-regulating pro-apoptotic factors might decrease brain damage in stroke victims (p. 326, right column, last paragraph). In addition, Lu et al. teach that caspase inhibition in combination with glutamate receptor antagonists (in order to decrease excitotoxic necrosis) could be used to decrease apoptosis and necrosis of neurons following stroke (see p. 204, last paragraph). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. and Bouma et al. by administering agents that control apoptotic and necrotic cell death, as taught in Tarkowski et al. and Lu et al. because apoptosis of neurons is thought to contribute to neuronal cell death (see Tarkowski, p. 325, right column, last paragraph to p. 326, left column, 1st paragraph). The person of ordinary skill in the art would have been motivated to combine the teachings because as outlined above, there

are only a limited number of available options for the clinician in the treatment of stroke. Furthermore, the person of ordinary skill in the art could have reasonably expected success because Lu et al. provide further evidence of how caspase inhibition (and decreasing apoptosis) combined with glutamate receptor antagonism (to prevent necrosis) could lead to less neuronal loss following ischemic injury and neurodegenerative disorders. Finally, since Bouma et al. teach that the pathophysiology of stroke and traumatic brain injury are the same and both involve neuronal death, the person of skill in the art would be motivated to administer an agent that decreases apoptosis to those suffering from ischemia due to traumatic brain injury as well as to those suffering from stroke.

Response to Arguments regarding Rejections under 35 U.S.C. 103(a)

The arguments presented by Applicants regarding Buschmann et al. are directed to the rejection under 35 U.S.C. 102(b), which has been withdrawn, thus will not be addressed here. Nevertheless, the following argument is relevant to all the rejections under 103:

Applicants' argue at p. 9, penultimate paragraph that Buschmann mentions the possibility of using GM-CSF, G-CSF, or M-CSF for the treatment of stroke, however, the mode of action described by Buschmann is arteriogenesis and neither traumatic brain injury nor the neuroprotective effects of G-CSF as disclosed in the instant application is taught by Buschmann.

This argument has been fully considered but is not found persuasive. , it is not necessary that the combined teachings appreciate the mechanism of action, only that

they suggest to the POSITA the treatment of TBI with G-CSF with a reasonable expectation of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1-19, 101-102 and 105 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-22 and 52-53 of copending Application No. 10/880,101 as set forth at pages 22-24 of the previous Office action mailed 29 January 2007 is maintained for reasons of record. Applicants' request deferral of this issue until other issues of patentability are resolved in their response filed 30 July 2007 is noted. However, deferral of arguments is not proper; an argument after the claims have been found otherwise allowable that

obviousness type double patenting does not exist will not be considered timely. Accordingly, the provisional rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 7:00am - 1:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646